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Review

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Advances in the Development of Therapeutic Strategies Against COVID-19 and Perspectives in the Drug Design for Emerging SARS-CoV-2 Variants

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Short Title: Advances and perspectives of therapeutic drugs in COVID-19 pandemic

Abstract

Since Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified in late 2019, the coronavirus disease 2019 (COVID-19) pandemic has challenged public health around the world. Currently, there is an urgent need to explore antiviral therapeutic targets and effective clinical drugs. In this study, we systematically summarized two main therapeutic strategies against COVID-19, namely drugs targeting the SARS-CoV-2 life cycle and SARS-CoV-2-induced inflammation in host cells. The development of above two strategies is implemented by repurposing drugs and exploring potential targets. A comprehensive summary of promising drugs, especially cytokine inhibitors, and traditional Chinese medicine (TCM), provides recommendations for clinicians as evidence-based medicine in the actual clinical COVID-19 treatment. Considering the emerging SARS-CoV-2 variants greatly impact the effectiveness of drugs and vaccines, we reviewed the appearance and details of SARS-CoV-2 variants for further perspectives in drug design, which brings updating clues to develop therapeutical agents against the variants. Based on this, the development of broadly antiviral drugs, combined with immunomodulatory, or holistic therapy in the host, is prior to being considered for therapeutic interventions on mutant strains of SARS-CoV-2. Therefore, it is highly acclaimed the requirements of the concerted efforts from multi-disciplinary basic studies and clinical trials, which improves the accurate treatment of COVID-19 and optimizes the contingency measures to emerging SARS-CoV-2 variants.

Keywords: SARS-CoV-2; COVID-19 pandemic; therapeutic strategies; drug target; SARS-CoV-2 variants

1. Introduction

The new coronavirus, namely 2019-nCoV, was first identified on December 31, 2019. Due to being highly homologous to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), 2019-nCoV was listed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Commission for Classification of Viruses (ICTV) on February 11, 2020 [1]. Among seven coronaviruses infecting humans, three coronaviruses can cause serious diseases, including severe acute respiratory syndrome coronavirus (SARS-CoV) emerging in 2003, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2019 [2].

The outbreak of SARS-CoV-2 causes an acute respiratory disease called coronavirus disease 2019 (COVID-19) and leads to a severe epidemic worldwide. Typical symptoms of COVID-19 include fever, sore throat, fatigue, cough, and difficulty breathing [3, 4]. Some of the clinical symptoms are similar to those of respiratory infections and cannot be accurately diagnosed. The approach to quickly diagnose and develop related drugs and vaccines has become a top priority. At present, the WHO has approved the use of a variety of vaccines [5]. As of January 9, 2022, the cumulative number of reported cases worldwide has exceeded 304 million, and the cumulative death toll has been more than 5.4 million [6]. As of January 13, 2022, a total of 9.2 billion doses of vaccine have been administrated globally (Figure 1).

Till now, there have been candidate drugs in COVID-19 treatment at different stages and levels available for selection and further research and development (Table 1). These small-molecule drugs can exert therapeutic effects against COVID-19 by preventing SARS-CoV-2 from entering cells, inhibiting viral proteases or RNA-dependent RNA polymerase activities, reducing virus-induced inflammation, and balancing immunomodulatory effect in host [7, 8]. Fortunately, some antiviral drugs have been used in clinical practice and play certain roles in the treatment of COVID-19 patients, such as Remdesivir and Molnupinavir [9-11]. Currently, hundreds of clinical trials of COVID-19 drugs are underway to obtain satisfactory clinical results [12]. A large number of promising clinical trials will determine which drugs or vaccines are suitable for the treatment or prevention of COVID-19 (Table 2).

The effective medicine is expected to be approved for COVID-19 treatment, however, due to the rapid mutation of SARS-CoV-2 genome, the present drugs or vaccines may lose their control on SARS-CoV-2 spread with the increased infectivity [13, 14]. The emerging SARS-CoV-2 variants bring severe challenges to COVID-19 surveillance and control. In this review, we systematically summarized the advances in the therapeutic strategies against COVID-19 targeting the structure of SARS-CoV-2 in viral life cycle and immune response in virus-host interaction. More importantly, we presented the details and clues of SARS-CoV-2 variants for further perspectives in drug design, which inspires follow-up researchers to develop therapeutic agents against pandemic COVID-19 and emerging SARS-CoV-2 variants.

2. The structure of SARS-CoV-2

SARS-CoV-2 is a kind of enveloped virus at a diameter ranging from 80-220 nm with a positive single-stranded RNA inside its shell, belonging to the β-CoV class of human coronaviruses [2]. The entire SARS-CoV-2 particle is mainly composed of 4 structural proteins, a fragile lipid envelop, and genomic RNA. The four structural proteins are the membrane (M), nucleocapsid (N), envelop (E), and spike (S) protein (Figure 2A).

The M protein plays a central role in virus assembly. Its presence enables viruses and host factors to gather on the cell membrane to form progeny virus particles [15]. The complex formed by N protein and genomic RNA plays an important role in viral transcription and assembly. The N protein is divided into N-terminal domain, C-terminal domain, and disordered central domain (NTD, CTD, and RNA binding domain) [16]. The E protein is a small and complete membrane protein, and its functions run through the life cycle of SARS-CoV-2, including assembly and pathogenicity [17]. The S protein is the key to the invasion of cells by SARS-CoV-2 and it exists on the surface of the virus membrane in the form of trimers [18]. It is composed of S1 and S2 subunits and the latter one is the most conserved region in spike protein [19]. The E protein and the M protein are alternately arranged on the surface of the virus membrane, together with the S protein forming the virus shell, and the N protein interacts with the viral RNA to form the core of the virus particle [2]. During viral replication, a polyprotein

1ab is translated through ORF1ab in viral genome, and subsequently cleaved into 16 non-structural proteins by protease (Figure 2B).

The proteins of SARS-CoV-2 are highly glycosylated [20]. For example, about 40% surface of S protein is covered by glycans [21], which helps the virus hide epitopes and avoid antibody recognition [22]. SARS-CoV-2 S protein comprises 22 N-linked glycosylation sequons per protomer [23]. Because glycosylation is the key to virus invasion, the glycosylation of S protein needs to be taken into consideration when designing vaccines and antibodies [24].

3. Life cycle of SARS-CoV-2

SARS-CoV-2 can bind to Angiotensin-converting enzyme 2 (ACE2), a functional receptor of SARS-CoV [25], on the cell surface with its S protein to enter the cell through membrane fusion and endocytosis [19] (Figure 3A). Proteins from host cells, such as the serine protease TMPRSS2 [26] and high-density lipoprotein (HDL) scavenger receptor type B (SR-B1) [27], facilitate the SARS-CoV-2 invasion processes (Figure 3B). Transmembrane serine protease 4 (TMPRSS4) is found to be most significantly related to ACE2 [28]. SARS-CoV-2 has its unique Furin cleavage site never found before in other coronaviruses, is required for the virus to enter cells lacking cathepsin protease [29]. Furin can cleave the SARS-CoV-2 spike protein at the S1/S2 site [2], resulting in active S1 and S2 subunits. The cutting process occurs during the virus packaging process [30].

Once entering the host cell, the virus particle releases the viral genome, and utilizes host ribosome to translate the viral polyproteins pp1a and pp1ab [31]. Then the viral protease 3CLpro [32] and PLpro [33] cleave the polyprotein into a variety of active proteins (Figure 3C). Viral replication is dominated by a replication/transcription complex composed of non-structural proteins [34]. For example, nsp7, nsp8, and nsp12 together form the virus-independent RNA polymerase structure (RdRp) for viral genome replication [35] (Figure 3D). The translation of nsp14 can shut down the host protein synthesis and inhibit the innate immune response, while the combination of nsp10 enhances this effect [36].

After four structural protein is produced by transcription, the N protein binds to the genome, and the remaining three (S, E, and M) are integrated into the endoplasm and then sent to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) for further process, such as furin-mediated cleavage. Subsequently, the assembled progeny virus was released by exocytosis or budding [37, 38] for the next round of invasion to host cell (Figure 3E). In ERGIC, E protein can form pores to cause Ca^{2+} to leak and activate NLRP3 inflammasome to achieve pro-inflammatory effects [39] (Figure 3F).

4. Drugs targeting the SARS-CoV-2 life cycle

The process of SARS-CoV-2 entering the human body and self-replicating to release progeny virus can be divided into different stages. According to the characteristics of each dynamic stage, different drug targets to these specialized processes are formulated to block the life activities of the virus (Figure 3).

4.1 Anti-viral entry

4.1.1 Inhibition of key enzymes in the binding process

Alpha-1 antitrypsin (α1AT) inhibits the protease activity of TMPRSS2 at physiological concentrations to restrain the entry and replication of SARS-CoV-2 in cell lines and primary cells [40]. A statistical study based on 500,000 people shows that mild α1-Antitrypsin deficiency (AATD) genotypes were not associated with increased SARS-CoV-2 infection rates or fatalities [41]. For the lack of α1AT makes it easier to activate TMPRSS2, severe AATD patients may be susceptible to SARS-CoV-2 [42, 43]. There have been four trials recruited or completed to test whether α1AT can be used for the treatment of COVID-19 patients [44].

Halofuginone can reduce endogenous TMPRSS2 expression at sub-micromolar concentrations, which showed significant resistance to SARS-CoV-2 infection in vitro in both live- and pseudo-virus models [45]. Halofuginone is an oral anti-fibrosis [46] and anti-inflammatory [47] drug. A study in mice reveals that the distribution of halofuginone can be detected in various organs, including kidneys and lungs [48]. ACE2 is widely expressed in these organs [49], making these organs vulnerable to the SARS-CoV-2. Therefore, the antiviral

activity and wide distribution of halofuginone in vivo repurpose it as a promising anti-SARS-CoV-2 drug.

Platycodon grandiflorum D (PD), a natural component of Platycodon grandiflorum [50], and pan-coronavirus fusion inhibitor EK1 derived lipopeptide EK1C4 [51] can effectively block SARS-CoV2-mediated membrane fusion to combat viral infections. Since TMPRSS2 is induced by androgens (AR), the AR anti-caking agent Proxalutamide (GT0918) can significantly accelerate virus clearance on day 7 in patients with mild to moderate COVID-19 [52].

4.1.2 Competitive binding to ACE2 and SARS-CoV-2 S protein

Catechin and curcumin have a strong binding affinity to the virus S protein and host receptor ACE2 and its complex, which can trigger local structural fluctuations of the protein through their binding with RBD/ACE2 complex [53]. In a study, using protein engineering technology, the self-assembled tetramerization domain from p53 protein produces a super tetravalent form of ACE2 coupled to the Fc region of human immunoglobulin γ1, the high-molecular-weight Quad protein (ACE2-Fc-TD) retains the binding to the ACE2 and its binding SARS-CoV-2 S protein and can form a complex with the S protein and antiviral antibodies as a bait protein [54]. Similarly, antibodies that bind to viral RBD epitopes (such as REGE-CoV) [55, 56] or that target the ACE2 receptor (such as h11B11) [57] can also effectively prevent and reduce the symptoms of viral infections. The viral load in the SARS-CoV-2 infected animals is significantly reduced after the single-dose h11B11 treatment, while the animals showed less interstitial pneumonia and limited pathological features under the preventive treatment conditions [57], which makes it a potential therapeutical agent in COVID-19.

4.2 Viral protease inhibitors

The organic selenium compound Ebselen and its structural analogs can inhibit the activity of the SARS-CoV-2 protein PLpro in the nanomolar range [45]. Two clinical trials of Ebselen are now recruiting moderate and severe COVID-19 patients [44]. There is also evidence that Catechin binds to the S1 ubiquitin-binding site of PLpro, which may inhibit its protease function

and cancel the inhibitory function of SARS-CoV-2 on the ubiquitin-proteasome system and the interferon-stimulated gene system [58].

The viral main protease Mpro is also a widely explored drug target. Two kinds of small molecule compounds with indole structure named GRL-1720 and 5h inhibit the main protein Mpro of the SARS-CoV-2, which can effectively block viral infections in vitro [59]. Another Mpro inhibitor, GC-376, is also a promising main candidate for further development of the treatment of SARS-CoV-2 infection [60]. GC-376 exhibits no toxicity in K18-hACE2 mice experiment, showing moderate benefits in terms of clinical symptoms, weight change, and survival rate. Under low-dose virus attack, GC-376 can prevent the virus from reaching the brain and reduce inflammatory cell distribution and virus staining [60]. However, the potential anti-inflammatory effect needs to be further developed.

4.3 Anti-viral RNA polymerase

The active form of Remdesivir, which has been approved for COVID-19 treatment, acts as a nucleoside analog [61] and inhibits RNA-dependent RNA polymerase (RdRp). Remdesivir is incorporated into the growing RNA product by RdRp [62], and the translocation barrier causes RNA 3'-nucleotide to remain at the substrate binding site of RdRp and interfere with the entry of the next nucleoside triphosphate, thereby stagnating RdRp [63]. Multiple trials have confirmed the effectiveness of Remdesivir treatment [64, 65]. Through binding to viral RdRp, other nucleoside analogs such as Ribavirin, Sofosbuvir, Galidesivir, Setrobuvir, and Tenofovir behave as potent drugs against SARS-CoV-2[66, 67]. Nevertheless, it is still a long way for these FDA-approved RdRp inhibitors to apply in COVID-19 from bench to bed.

So far, it has always been the top priority of scientists to find a convenient, effective, and low-cost oral drug against COVID-19 because of the expensive monoclonal antibodies. On December 22, 2021, the FDA issued an emergency use authorization for Pfizer's Paxlovid, and on the following day, it urgently approved Merck's Molnupiravir [68]. Paxlovid is composed of Nimarivir (PF-07321332) and low-dose Ritonavir. Pfizer claims that compared with placebo treatment group, the risk of hospitalization or death in non-hospitalized adults at high risk of COVID-19 treated with Paxlovid was reduced by 89%. Nimarivir is a SARS-CoV-2 3CLpro

inhibitor and can reduce virus replication [69]. Ritonavir can alleviate the degradation of Nimarivir and keep it at a higher concentration for a long duration as possible [70]. Recently, the oral antiviral drug Molnupiravir, an inhibitor of RdRp leading to viral fatal mutations or premature termination of replication [71], has attracted attention and expectation. Although Molnupirivir is reported host mutation activity in animal cell culture experiments [72], the safety of molnupiravir was confirmed in a drug safety assessment [73].

4.4 Anti-viral release

The assembled progeny of SARS-CoV-2 is released by exocytosis or budding [37, 38]. Oseltamivir is a prodrug against neuraminidase inhibitor, which has been approved for the treatment and prophylaxis of influenza A by inhibiting the release of progeny virion by budding from the infected cells[74]. In both in vitro and in vivo studies, Oseltamivir is ineffective against SARS-CoV-2 and fails to improve the patients' symptoms and signs in the clinic [75].

SARS-CoV-2 infected cells express Spike protein (S) on their surface and fuse with ACE2-positive neighboring cells. The expression of SARS-CoV-2 S protein in the absence of any other viral proteins triggers the formation of syncytia [76] and determines syncytium-mediated lymphocyte elimination [77]. The anti-helminth drug Niclosamide was found to significantly reduce the calcium oscillation and membrane conductance in cells expressing spikes [78], which interferes with the syncytial formation process induced by S protein. A trial proved that Niclosamide has relatively safe clinical benefits in COVID-19 management. Compared with the control group, the cure rate of the Niclosamide treatment group increased [79]. Niclosamide has poor oral bioavailability due to its limited water solubility. Therefore, considering the economic issues of treatment, it is necessary to explore its effective use.

5. Drugs targeting SARS-CoV-2-induced inflammation in host cells

Inflammation is an early response triggered by harmful stimuli and conditions to restore homeostasis. SARS-CoV-2 could evoke the immune system and induce pro-inflammatory factors such as IL-6, IL-1, TNF-α, and IFN [80-82] overproduction called a cytokine storm,

which brings catastrophic damage to cells and then causes dysfunction and failure of tissues and organs [83]. The levels of cytokines in critical COVID-19 patients are significantly higher than those in mild conditions [84]. SARS-CoV-2 infection can cause cytokine release syndrome (CRS) [85], which then produces a series of consequences such as multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), and even death [86] [87]. The intervention and treatment of cytokine storm are necessary means to reduce COVID-19 mortality (Figure 4).

5.1 Cytokine inhibitors

Overdose of interleukin-6（IL-6）is one of the causes of cytokines storm in COVID-19 [88]. Tocilizumab (TCZ) is the first IL-6 receptor inhibitor discovered, which reduces the immune damage caused by IL-6 to target cells by competitively binding to IL-6 receptors [89]. Shreds of evidence have shown that in a limited number of patients, symptoms, hypoxemia, and changes in chest tomography (CT) opacity in patients treated with TCZ are immediately improved [90]. Results from a primary intention-to-treat (ITT) phase 2 population shows that TCZ may reduce lethality rates at 30 days [91]. In a meta-analysis, however, there was no difference in mortality between the TCZ treatment group and the placebo group. TCZ can reduce the length of hospital stay while the impact on survival has not been statistically proven, but the combined use of corticosteroids is found enable to optimize the proven effectiveness of corticosteroids [92]. Hence, to better use TCZ in COVID-19 treatment, the combination of medication can be taken into consideration.

Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist with anti-inflammatory and immunomodulatory effects [93]. A study has revealed that Anakinra significantly reduces the mortality and the ICU invasive mechanical ventilation needs of COVID-19 patients [94]. An updated meta-analysis shows that Anakinra can reduce the 50% risk of death in hospitalized patients with moderate to severe COVID-19 compared with patients untreated with Anakinra [95]. Chloroquine owns an immunomodulatory effect, inhibiting the production and release of TNF-α and IL- 6 [96], which may modulate cytokine storm in COVID-19 [97, 98]. However, it has not been shown to benefit COVID-19 patients in randomized controlled trials [99].

Sarilumab is another IL-6 blocker [100, 101], a fully human immunoglobulin G1 monoclonal antibody with a high affinity for membranes and IL-6 receptors [102]. A retrospective case from an institution in southern Italy showed that 10 COVID-19 patients (67%) observed rapid improvement in their respiratory parameters after using Sarilumab [103]. In the results of the Sarilumab at a safe dose of 400 mg and placebo groups, the COVID-19 patient mortality rates were 23% and 27%, while the hospital discharge rates were 53% and 41%, respectively [102].

Canakinumab is an IL-1 blocker developed by Novartis for the treatment of inflammatory diseases [104]. In a study of 48 patients with moderate COVID-19-related pneumonia, Canakinumab was found to reduce the need for invasive mechanical ventilation. 63% of patients in the Canakinumab group were discharged within 21 days while the control group was 0% [105]. For mild or severe COVID-19 pneumonia, a study has observed a decrease in the inflammation index in the Canakinumab group, which can lead to a rapid and lasting improvement in oxygenation levels [106].

With IL-12 or IL-15, IL-8 can be an effective inducer of IFN-γ in certain kinds of cells [107]. The combination of TNF-α and IFN-γ can strongly induce cell death characterized by inflammatory cell death [108]. In COVID-19 patients, these uncontrolled expressions of cytokines can cause excessive damage to tissues and organs[109]. As a result, inhibitors of abnormally increased levels of cytokines can be used as potential drugs for COVID-19 treatment. Meanwhile, due to the existence of synergistic effects, combination drugs or multi-targets can be considered view of drug development. However, the combinate use of corticosteroids is still controversial. While inhibiting inflammation, it also stops the elimination of the virus and causes a series of side effects [110, 111].

5.2 Signaling pathway inhibitors.

Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway is essential for the development and function of the immune system [112], which are involved in the various pro-inflammatory factors [113]. Therefore, the use of JAK inhibitors is one of the ideas to reduce the cytokine storm in COVID-19. Baricitinib and Ruxolitinib are potent and

selective JAK inhibitors approved for indications such as rheumatoid arthritis and myelofibrosis [114], which are currently reused for the treatment of SARS-CoV-2 infected patients. Studies have confirmed the safety and effectiveness of these drugs in reducing cytokine levels in the treatment of COVID-19 as antiviral drugs [115-117]. In addition, Baricitinib has the effect of reducing the endocytosis of the SARS-CoV-2 [118]. The combined use of Baritinib and Remdesivir can shorten the recovery time and accelerate the improvement of clinical status, especially for patients receiving high-flow oxygen or non-invasive ventilation [119].

The nuclear factor NF-κB pathway is a classic pro-inflammatory signaling pathway [120]. The inhibition of NF-κB signaling has therapeutic applications in cancer and inflammatory diseases [121], as well as virus- and LPS- induced cytokine storms [122]. The use of NF-κB inhibitors Caffeic acid phenethyl ester (CAPE) and Parthenolide can improve the survival rate of mice infected with SARS-CoV [123]. Considering the spike protein of coronavirus upregulates IL-6 and TNF-α in murine macrophages through the NF-κB pathway [124], the exploration of NF-κB inhibitors may be an effective measure to reduce the cytokine storm upon SARS-CoV-2 infection. Although some studies have found potential new drugs that can be used to inhibit NF-κB to inhibit SARS-CoV-2 infection, [125, 126], whether they can be applied to the treatment of COVID-19 remains to be investigated.

In a trial to screen drugs with SARS-CoV-2-related pangolin coronavirus model, the Cepharanthine (CEP) showed a significant antiviral effect [127]. CEP inhibits viral replication by modulating signaling pathways [128, 129], among which it exhibits anti-inflammatory effects through AMPK activation and NF-κB inhibition[130]. Another study also confirmed the antiviral effect of CEP, and the combination of CEP and Nelfinavir can enhance their efficacy [131]. Existing evidence shows that CEP has important potential value in the treatment of COVID-19 [132], it still needs further verification by in vivo experiments and clinical trials.

5.3 Steroids treatment

Pidotimod is a synthetic dipeptide molecule, which has biological and immunological activity on both the adaptive and the innate immune responses [133]. Pidotimod can increase the

expression of NF-κB protein without an increase of IL-8 expression [134]. Pidotimod has been evaluated as an immunostimulant for respiratory infections (RTIs) [135] and the treatment of many other diseases [136]. A controlled experiment involving 20 COVID-19 patients showed that Pidotimod can effectively improve the fever of patients and prevent the activation of the cytokine cascade [137].

Viral infections usually cause excessive hyperinflammation [138]. The anti-inflammatory effect of steroids can stabilize hemodynamics and shorten the stay time of the intensive care unit (ICU) and the duration of mechanical ventilation. The use of steroids has always been controversial. Steroids can significantly reduce anti-inflammatory factors and may also delay virus clearance [139]. Long-term use of steroids can cause many adverse events, such as secondary infections [140]. In addition, The correlation between steroids and mortality remains unclear [141]. Steroids are currently used in critically ill patients to reduce clinical deterioration. One meta-analysis shows that the use of steroids is associated with higher mortality [142], whereas another prospective meta-analysis of seven randomized trials showed that the use of systemic corticosteroids was associated with lower all-cause mortality from COVID-19 [143]. The contradictory results indicate that there is still uncertainty in the role of corticosteroids, and more randomized controlled trials are needed to prove its effectiveness.

It is undeniable that corticosteroids have been widely used in the treatment of severe COVID-19 cases [144]. A trial showed that the 28-day mortality is reduced in COVID-19 patients receiving respiratory support after receiving up to ten days of dexamethasone treatment, which is useless for patients who do not require respiratory support [145]. The use of cedemethasone can reduce lung damage in COVID-19 patients [146], which is recognized by WHO in the clinical trial [147]. Whether other steroids have the same effects as dexamethasone is still unknown [148]. The combination of other drugs may alleviate the side effects of steroid use. An observational cohort study found that the combination of Barectinib and corticosteroids in the COVID-19 treatment can significantly improve lung function compared with corticosteroids alone [149]. Nonetheless, how to maximize the drug effect with a lower dose and shorter treatment time is another urgent problem that needs to be solved.

5.4 Holistic therapy and traditional Chinese medicine treatment

Rehabilitation plasma therapy can be taken in the early stage of COVID-19 by using antibodies in the convalescent serum to neutralize the virus to reduce the body damage caused by the immune system [150]. After the occurrence of cytokine storm, patients will have a variety of symptoms, such as MODS and ARDS. At this stage, anti-shock treatment is required to maintain the patient's body homeostasis and protect important organ functions.

In addition to conventional treatment, traditional Chinese medicine (TCM) plays an important role as an auxiliary method in clinical COVID-19 treatment, which has been confirmed to have antiviral activity against various coronavirus strains [151]. TCM treatment can improve clinical efficacy and alleviate COVID-19 patients' severe conditions [152, 153]. Since TCM recipes were according to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) [154], 92% of all of the confirmed cases in China had taken TCM in COVID-19 treatment [155]. Different recipes are recommended for different severity of conditions in COVID-19 treatment. Namely, Lianhua Qingwen (LHQW), Jinhua Qinggan (JHQG), Hua Shibaidu Granules (HSBD), Xuanfeibaidu Granules (XFBD), Xuebijing Injection (XBJ), and Qingfei Paidu Decoction are common TCM recipes [155].

In Vero cells, LHQW reduced the mRNA expression of pro-inflammatory cytokines TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10 [156]. A comparative study of multiple combination medications shows that the quadruple combination with LHQW can be the first choice for the treatment of patients in critical condition [157]. In detail, Rhein, forsythoside A, forsythoside I, neochlorogenic acid and its isomers may be the effective active ingredients of LHQW against SARS-CoV-2 [158]. A retrospective analysis of JHQG treatment promotes the absorption of pneumonia permeate with a higher 7-day viral clearance rate compared with the control group [159]. HSBD is suitable for early COVID-19 treatment [160], while XBJ is mainly used for patients in critical conditions [161]. The XBJ may relieve systemic inflammation by inhibiting the secretion of pro-inflammatory cytokines mediated by the HMGB1/RAGE axis to reduce mortality [162, 163].

Traditional Chinese medicine has played a huge role in China's anti-COVID-19 epidemic battle. However, there are many unsolved issues for Chinese scientists and researchers to precise the administration of TCM in COVID-19 treatment in the future. The concerning characteristics of TCM treatment are that the types and dosages of medications often change due to the different conditions of different patients. The molecular mechanisms of most TCMs are unclear, which raises the limitations in the global promotion of TCM against COVID-19 pandemic. Notably, the standardization behind different kinds of traditional Chinese medicines with various functions is highlighted and needs to be concerned.

6. Emerging SARS-CoV-2 variants

SARS-CoV-2 has been continuing to evolve, posing higher infectivity efficiency and faster transmission, leading to a greater risk to global public health. To better assess the consequences of different variants and facilitate prevention measures or medical countermeasures, WHO divides them into variants of interest (VOI) and variants of concern (VOC) [164]. There are currently two VOIs: Kappa and Mu; and five VOCs: Alpha, Beta, Gamma, Delta, and Omicron (Table 3). On November 24, 2021, a new SARS-CoV-2 variant B.1.1.529 named Omicron was discovered in South Africa. Previously, the SARS-CoV-2 Delta variant has become the main epidemic strain in many countries [165]. Now, the emergence of omicron has aroused new attention and vigilance. The mutations in Omicron are concentrated in the S protein, and there seems to be a tendency to collect mutations that are beneficial to immune escape [166, 167]. A model predicts and calculates that Omicron's infectivity is about ten times that of the original virus or twice that of the Delta variant. Omicron may greatly undermine the efficacy of the Eli Lilly monoclonal antibody (mAb) approved by the FDA, and may also reduce the efficacy of mAbs from Celltrion and Rockefeller University [168]. The main SARS-CoV-2 variants reported in different places worldwide create new concerns about anti-viral drugs and vaccinations against COVID-19 pandemic (Figure 5). The following critical mutation sites in SARS-CoV-2 genome determine the virulence and spread of the SARS-CoV-2 (Table 4), which provides fresh ideas in the drug design for the main emerging variants.

6.1 Mutations in structural proteins

D614G mutation in S protein will not significantly change the neutralizing properties of antibodies against SARS-CoV-2, and the currently developed vaccine against wildtype is still effective against the D614G strain [169]. The presence of the E484K mutation located in the receptor-binding domain (RBD) of the S protein will reduce the neutralizing power of a variety of effective mAbs that change the receptor-binding motif on RBD [170]. The introduction of E484K mutations into other variant strains will also lead to a decrease in the neutralization of antibodies and monoclonal antibodies caused by the vaccine [171]. N501Y mutation found in the British variant strain B.1.1.7 has almost no effect on the neutralizing effect of neutralizing nanobodies (Nbs) [172]. However, the mutant strain often accompanies other key amino acid mutations that affect the binding of S protein to ACE2. L18F mutation occurs in the NTD region and can cancel the binding of S2L28 monoclonal antibody to NTD [173] and the L18F mutation is positively correlated with mortality [174]. K417N mutation, close to the ACE2 binding site, is slightly detrimental to ACE2 binding [171], but it can promote the process of variants effectively avoiding antibodies by eliminating the buried interface salt bridge between RBD and neutralizing antibody CB6 [175]. L452R mutation locates in the RBD hydrophobic plaques of the spike protein [176]. It will increase the affinity of the spike protein to ACE2 and is kind of destructive to NAb binding [177] and make the virus evade the monoclonal antibody LY-CoV555 [178]. P681R is a mutation near the furin-cleavage site [179], which enhances the cleavage of S1 and S2 by the full-length spike, resulting in increased infection through the cell surface [180].

6.2 Mutations in non-structural proteins

Among the SARS-CoV-2 nonstructural proteins (nsp), virus-associated enzymes such as RdRp and 3C are important drug targets [181]. Mutations at these sites may increase virus resistance to related drugs [182, 183]. Mutations in RdRp, for example, may reduce the effect of Remdesivir. Studies have shown that the 14408 C>T mutation increases the viral mutation rate,

while 15324 C>T has a reduced effect [184]. Mutations in nsp may correlate with the degree of symptoms caused by SARS-CoV-2. A study found that mutations located in the nsp6 coding region were significantly associated with asymptomatic COVID-19 [185], which could make it difficult to initially screen COVID-19 patients. Different nsps have their structures and functions, which can be changed by the mutations [186]. For example, the V121D mutation in nsp1 may have a disruptive effect on it, and the G1691C in Nsp3 reduces the flexibility of the protein [187]. Therefore, these mutations in nsps should be taken into account in drug and vaccine development or treatment against COVID-19.

7. Perspectives in the drug design for SARS-CoV-2 variants

The current SARS-CoV-2 genome site mutations are all subject to natural selection and drug screening, which reflect the adaptation of the virus to the treatments. Some mutations make the virus increase the infectivity and transmission, however, in terms of treatment, the previous drugs are still effective against SARS-CoV-2 variants [188]. Other mutations render part of the antibody ineffective against SARS-CoV-2 [189], and the virus escapes from immunity, which brings new challenges to treatment. Therefore, the exploration of broadly antiviral drugs is prior to being concentrated and developed. More importantly, the immunomodulatory and holistic therapy in host, including anti-inflammatory strategies and Chinese traditional medicine treatment, should be concerned in the drug design for SARS-CoV-2 variants.

The binding of SARS-CoV-2 S protein to the ACE2 receptor is a key activity for the virus to invade the human body, and most of the mutation sites that are currently being studied are located in the S protein [190]. Researchers need to test one by one to determine the impact of specific mutation sites on the life of the SARS-CoV-2 and then test whether the previous treatments such as monoclonal antibodies are still effective for the emerging variants. However, a SARS-CoV-2 variant often carries a combination of different mutation sites and becomes a multiple mutant strain, and the speed of mutation is rapid [177]. It is of high concern that the effects from different combinations of mutation sites will have on viral infection activities. As

a result, the highly conservative sites of the SARS-CoV-2 genome as drug targets could be paid more attention to maintaining antiviral activities against variants.

8. Discussion

SARS-CoV-2 has caused a global pandemic since late 2019. With the increase of experience and knowledge, defensive measures and clinical treatment plans are adopted immediately according to observation and management of COVID-19 pandemic. Meanwhile, researchers are exploring more possibilities of repurposing drugs against SARS-CoV-2 [191]. However, the development of specific drugs and vaccines requires fundamental studies on SARS-CoV-2, such as the interaction between the virus and the host, the epidemiology and molecular virology, the host immune responses to viral infection, to uncover the mechanism underlying the infection, transmission, and pathogenesis of the virus and explore effective drugs.

Traditional Chinese medicine has played a huge role in China's anti-epidemic process [192]. Research on the mechanism of action of traditional Chinese medicine may provide new ideas for the development of anti-SARS-CoV-2 drugs. At the same time, it is necessary to pullulate holistic treatments to deal with the systemic pathological imbalance caused by the SARS-CoV-2.

Owing to the error-prone RNA replicase of SARS-CoV-2 [193], the continuous emergence of mutant strains has undoubtedly brought huge difficulties and challenges to the control of the global COVID-19 epidemic. The appearance of SARS-CoV-2 variants means that the virus adapts to manual interventions and natural selection, which may eliminate the effectiveness of previous drugs and vaccines. In this case, we must maintain epidemiological surveillance of COVID-19 timely and focus on the evolution of the virus, especially the emergence of drug-resistant strains.

The pathogenesis of COVID-19 can be mainly divided into two phases [194]. In the early stage, the COVID-19 patients may begin with a series of mild symptoms including fever, cough, fatigue, hemoptysis, headache, or diarrhea, and then will develop pneumonia [155, 195]. Accordingly, antiviral drugs can be given to clear the virus from the body of patients infected

with SARS-CoV-2. Later on, as the viral load increases and spreads in the human body, which triggers excessive production of cytokines, a cytokine storm occurs in the COVID-19 patients to deteriorate to moderate and severe symptoms with respiratory distress syndrome and organ failure [196, 197]. It should be necessary to adopt antiviral drugs with immunomodulatory treatment, and also encouraged to introduce holistic therapy and traditional Chinese medicine treatment, and even external mechanical equipment and maintain the normal operation of the patient's body [198].

In sum, SARS-CoV-2 mutation is an urgent issue that needs to be explored and solved, which requires concerted efforts from the fields of structural biology, medicine, virology, pharmacy, public health, epidemiology, chemistry, and other disciplines, to jointly deal with the treatment and control of COVID-19 pandemic.

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Figures and figure legends

Figure 1. Update of COVID-19 pandemic worldwide.

As of January 9, 2022, the cumulative number of reported cases worldwide had exceeded 304 million, while the cumulative death toll had exceeded 5.4 million. Till to January 13, 2022, 9.2 billion doses of vaccine have been administered globally.

Figure 2. The morphologic and genomic structure of SARS-CoV-2.

(A) SARS-CoV-2 is an enveloped virus consisting of spike protein (S), envelope protein (E), membrane protein (M), nucleic acid protein (N), and single-stranded RNA in the virion. (B) The genomic RNA of SARS-CoV2 is linear, positive-sense, and single-stranded with the length of approximately 30 kb, which contains a 5' cap and 5'UTR cap, open read frame (ORF), followed by 3'UTR and poly(A) tail. The largest gene, ORF1ab, encodes the pp1ab protein containing 15 nsps (nsp1 to nsp10 and nsp12 to nsp16). The pp1a protein encoded by ORF1a gene also contains 10 nsps (nsp1 to nsp10). Structural protein is encoded by 4 structural genes, including S protein, E protein, M protein, and N protein encoding genes. Accessory genes, encoding accessory proteins such as nsp3a and nsp6p, are distributed in structural genes.

Figure 3. The life cycle of SARS-CoV-2.

The entry of SARS-CoV-2 is initiated through that TMPRSS2 acts on the S protein to activate the S1 and S2 subunits. The S1 subunit binds to the ACE2 receptor to occur endocytosis (A), and S2 mediates membrane fusion (B). Subsequently, the virus releases its genomic RNA, which is translated into viral polyprotein by the ribosome of the host cell. Under the action of lysosomal cathepsin, the virus releases genomic RNA and then is translated into viral polyprotein, subsequently cleaved into nonstructural proteins (nsp) with viral proteases including 3CLpro and PLpro (C). SARS-CoV-2 RdRp replicates and amplifies a large number of viral genomes, and then is transcribed and translated into four structural proteins (D). The progeny genome and structural proteins are assembled on endoplasmic reticulum-Golgi intermediate compartment (ERGIC), which are transported and released to the outside of host cell (E). The furin on the Golgi apparatus cleavages and pre-activates the S protein. Infected

cells can fuse with neighboring cells to form syncytia. In addition, E protein in ERGIC can form pores to cause Ca^{2+} to leak to achieve pro-inflammatory effects (F).

Figure 4. Summary of therapeutic targets to SARS-CoV-2-induced inflammation in host cells.

SARS-CoV-2 could evoke the immune system and trigger cytokine release syndrome (CRS) and cytokine storm, leading to multiple organ dysfunction syndrome (MODS) and acute respiratory distress syndrome (ARDS), and even death. The therapuetic inventations are introduced to alleviate inflammation to reduce the severity of COVID-19.

Figure 5. The appearance of mutant strains of SARS-CoV-2 around the world.

The main emerging SARS-CoV-2 variant strains are classified as VOC (variants of concern), VOI (variants of interest), and VUM (variants under monitoring). VOC includes Alpha, Beta, Gamma, Delta, and Omicron; VOI contains Lambda and Mu, while VUM includes Theta, Eta, Iota, and Kappa from the public data (https://outbreak.info/situation-reports#custom-report, as of 26 November 2021). The time of appearance is expressed as yy/mm.

Tables

Table 1 Summary of approved and developed drugs against COVID-19.

Approved drugs				
Product	**Developer**	**Therapeutic class/drug type**	**Status**	**Approving Authority**
Kineret (Anakinra)	Sobi	Immunomodulator	Marketing authorization granted: 17/12/2021	EMA
Regkirona (Regdanvimab)	Celltrion Healthcare	Monoclonal antibody	Marketing authorization granted: 12/11/2021	EMA
RoActemra	Roche	Immunomodulator	Marketing authorization for COVID-19 indication granted: 07/12/2021	EMA
Ronapreve (Casirivimab/ Imdevimab)	Roche & Regeneron	Monoclonal antibody	Marketing authorization granted: 12/11/2021	EMA
Veklury (Remdesivir)	Gilead Sciences	Nucleotide analogs	Conditional marketing authorization granted: 03/07/2020	EMA
			Marketing authorization granted: 22/10/2020	FDA
Xevudy (Sotrovimab)	GlaxoSmithKline & Vir Biotechnology	Monoclonal antibody	Marketing authorization granted: 17/12/2021	EMA
Developed drugs				
Product	**Developer**	**Therapeutic class/drug type**	**Status**	**Data source**

Sarilumab	Sanofi Aventis	Immunomodulator	Clinical phase	EMA
Canakinumab	Novartis	Monoclonal antibody	Clinical phase	Clinical trials
Anakinra	Swedish Orphan Biovitrum AB (SOBI)	Immunomodulator	Clinical phase	EMA
Tocilizumab	Roche	Immunomodulator	Clinical phase	EMA
Pidotimod	/	Immunomodulator	/	/
Cepharanthine	/	Immunomodulator	/	/

The information is summarized from the available data online at sites https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs, https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-research-development, and https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=anakinra&cntry=&state=&city=&dist=. EMA: European Medicines Agency; FDA: the U.S. Food and Drug Administration.

Table 2 Summary of approved COVID-19 vaccines.

Name of Vaccine	NRA of record	Type
Comirnaty (developed by Pfizer and BioNTech)	EMA/FDA	mRNA vaccine
COVID-19 Vaccine Janssen	EMA	Adenovirus vector vaccine
Nuvaxovid	EMA	Recombinant protein vaccine
Spikevax (previously COVID-19 Vaccine Moderna)	EMA	mRNA vaccine
Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	EMA	Adenovirus vector vaccine
Moderna COVID-19 Vaccine	FDA	mRNA vaccine
Janssen COVID-19 Vaccine	FDA	Adenovirus vector vaccine
SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	NMPA	Inactivated vaccine
COVID-19 Vaccine (Vero Cell), Inactivated/CoronavacTM	NMPA	Inactivated vaccine
Ad5-nCoV	NMPA	Recombinant protein vaccine
Recombinant Novel Coronavirus Vaccine (CHO Cell)	NMPA	Recombinant protein vaccine
SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	NMPA	Inactivated vaccine

NRA: National Regulatory Authority; EMA: European Medicines Agency; FDA: the U.S. Food and Drug Administration; NMPA: National Medical Products Administration.

Table 3. Detailed information on emerging SARS-CoV-2 variants.

VOC			
WHO Label	Pango lineage	Earliest Documented Samples	Key Mutation Sites
Alpha	*B.1.1.7*	United Kingdom in Sep-2020	DEL69/70; DEL144/145; N501Y; A570D; D614G; P681H; T716I; S982A; D1118H
Beta	*B.1.351*	South Africa in May-2020	D80A; D215G; DEL241/243; K417N; E484K; N501Y; D614G; A701V
	B.1.351.2		L18F; D80A; D215G; DEL241/243; K417N; E484K; N501Y; D614G; A701V
	B.1.351.3		
Gamma	*P.1*	Brazil in Nov-2020	L18F; T20N; P26S; D138Y; R190S; K417T; E484K; N501Y; D614G; H655Y; T1027I; V1176F
Delta	*B.1.617.2*	India in Oct-2020	T19R; G142D; E156G; DEL157/158; L452R; T478R; T478K; D614G; P681R; D950N
	AY.1		T19R; W258L; K417N; L452R; T478K; D614G; P681R; D950N
	AY.2		T19R; V70F; E156G; DEL157/158; A222V; K417N; L452R; T478K; D614G; P681R; D950N
	AY.3		T19R; E156G; DEL157/158; L452R; T478K; D614G; P681R; D950N
Omicron	*B.1.1.529*	South Africa in Nov-2020	A67V; DEL69/70; T95I; G142D; DEL143/145; T547K; D614G; H655Y; N679K; P681H; D796Y; N856K; Q954H; N969K; L981F
	BA.1		A67V; DEL69/70; T95I; G142D; DEL143/145; N211I; DEL212/212; G339D; S371L; S373P; S375F; S477N; T478K; E484A; Q493R; G496S; Q498R; N501Y; Y505H; T547K; D614G; H655Y; N679K; P681H; D796Y; N856K; Q954H; N969K; L981F
	BA.2		T19I; L24S; DEL25/27; G142D; V213G;

			G339D; S371F; S373P; S375F; T376A; D405N; R408S; K417N; N440K; S477N; T478K; E484A; Q493R; Q498R; N501Y; Y505H; D614G; H655Y; N679K; P681H; N764K; D796Y; Q954H; N969K
	BA.3		A67V; DEL69/70; T95I; G142D; DEL143/145; N211I; DEL212/212; G339D; S371F; S373P; S375F; D405N; S477N; T478K; E484A; Q493R; Q498R; N501Y; Y505H; D614G; H655Y; N679K; P681H; N764K; D796Y; Q954H; N969K
VOI			
Lambda	C.37	Peru in Dec-2020	G75V; T76I; R246N; DEL247/253; L452Q; F490S; D614G; T859N
Mu	B.1.621	Columbia Oct-2020	T95I; Y144S; Y145N; R346K; E484K; N501Y; D614G; P681H; D950N

The mutations of amino acid in SARS-CoV-2 S protein are presented. The summarized information represented in the table was derived from the public data (https://outbreak.info/situation-reports#custom-report, as of 26 November 2021).

Table 4. Mutations of concern and interest reports in SARS-CoV-2 variants.

Mutation of Concern Reports		
Mutation	Prominent in VOC	Prominent in VOI
E484K	B.1.351; B.1.351.2; B.1.351.3; P.1	B.1.621
Mutation of Interest Reports		
Mutation	Prominent in VOC	Prominent in VOI
L18F	B.1.351.2; B.1.351.3; P.1	/
K417N	B.1.351; B.1.351.2; B.1.351.3; AY.1; AY.2; BA.2	/
K417T	P.1	/
L452R	B.1.617.2; AY.1; AY.2; AY.3	/
N501Y	B.1.1.7; B.1.351; B.1.351.2; B.1.351.3; P.1; BA.1; BA.2; BA.3	B.1.621
P681R	B.1.617.2; AY.1; AY.2; AY.3	/

The mutations of amino acid in SARS-CoV-2 S protein are presented. The summarized information represented in the table was derived from the public data (https://outbreak.info/situation-reports#custom-report, as of 26 November 2021).

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